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(54) DEXTRIN CONTAINING COMPOSITIONS FOR PREVENTION OF ADHESIONS

DEXTRINHALTIGE ZUSAMMENSETZUNGEN ZUR VERMEIDUNG VON ADHÄSIONEN

COMPOSITIONS CONTENANT DE LA DEXTRINE DESTINEES A PREVENIR LES ADHESIONS

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Description

[0001] The present invention relates to the prevention of adhesions, and in particular to adhesions formed in serous cavities such as the peritoneum, the pericardium, the plura and synovial cavities such as joints and tendons, the adhesions being formed as a result of an inflammatory response. Reference will be made hereinbelow to the prevention of adhesions in the peritoneum but it should be understood that the present invention has applicability in connection with other serous cavities in both humans and animals.

Background to the Invention

[0002] Adhesions are typically formed in response to mechanical/surgical insult. They are a well documented post-surgical event. It is known to ameliorate the condition by introducing film-forming biocompatible agents into the body cavity around the area of the wound. However, we have found surprisingly that adhesions can also occur in patients suffering from ovarian cancer who receive chemotherapeutic agents via the i.p. route. In other words the adhesions are not formed in response to post-operative events. We believe that it is the chemical insult of the chemotherapeutic agent itself, rather than the possible mechanical injury by i.p administration that induces adhesion formation in these patients. These unexpected observations, we believe, are due to an inflammatory response in these patients to the drugs which they receive. The present invention seeks to provide a composition for use in preventing adhesions that are formed as a result of the inflammatory response.

[0003] WO 99 58168 A discloses dextrin compositions for the treatment of prevention of surgical adhesions.

[0004] The treatment of patients with inflammation has two primary objectives, the first being to relieve pain which is typically the presenting problem, and the second is to reduce/halt the tissue-damaging process. Conventional treatment for acute and/or chronic inflammation is to administer non-steroidal anti-inflammatory drugs or glutocorticoids, however administration of these classes of pharmaceutical can cause undesired side effects in some individuals and even dependency.

Statement of the Invention

[0005] According to a first aspect of the present invention there is provided the use of a composition comprising an aqueous formulation of dextrin for the manufacture of a medicament for the treatment of adhesions that are formed as a result of an inflammatory response to an agent selected from a chemotherapeutic or gene therapy agent or antibiotic or antiviral agent or an agent which causes an inflammatory response.

[0006] Reference herein to an inflammatory response is intended to include chronic inflammatory conditions, such as and without limitation, pelvic inflammatory disease, arthritis, chronic inflammatory bowel disease, ulcerative colitis, Crohn's disease, irritable bowel syndrome and/or acute inflammatory conditions such as those induced by tissue injury the tissue injury being as a result of chemical insult.

[0007] The term "dextrin" means a glucose polymer which is produced by the hydrolysis of starch and which consists of glucose units linked together by means mainly of α-1,4 linkages. Typically dextrins are produced by the hydrolysis of starch obtained from various natural products such as wheat, rice, maize and tapioca. In addition to α-1,4 linkages, there may be a proportion of α-1,6 linkages in a particular dextrin, the amount depending on the starch starting material. Since the rate of biodegradability of α-1,6 linkages is typically less than that for α-1,4 linkages, it is preferred that, for many applications, the percentage of α-1,6 linkages is less than 10% and more preferably less than 5%.

[0008] Any dextrin is a mixture of polyglucose molecules of different chain lengths. As a result no single number can adequately characterise the molecular weight of such a polymer. Accordingly, various averages are used, the most common being the weight average molecular weight (Mw) and the number average molecular weight (Mn). Mw is particularly sensitive to changes in the high molecular weight content of a polymer whilst Mn is largely influenced by changes in the low molecular weight content of the polymer.

It is preferred that the Mn of the dextrin is in the range of from 1,000 to 30,000 and ideally the Mw is in the range of from 3,000 to 50,000. More preferably, the Mn is from 3,000 to 8,000 and the Mw is from 5,000 to 50,000.

[0009] The term "degree of polymerisation" (DP) can also be used in connection with polymer mixtures. For a single polymer molecule, DP means the number of glucose units. For a mixture of molecules of different DP's, weight average DP and number average DP correspond to Mw and Mn. In addition, DP can also be used to characterise a polymer by referring to the polymer mixture having a certain percentage of polymers of DP greater than a particular number or less than a particular number.

[0010] It is preferred that the dextrin contains more than 15% of polymers of DP greater than 12 and, more preferably, more than 50% of polymers of DP greater than 12.

[0011] The dextrin used in the present invention is water soluble or at least forms a suspension in water or a gel formulation. The dextrin used in this invention may be in the form of either unsubstituted dextrin (as obtained by the

hydrolysis of starch) or may be substituted by one or more different groups. The substituents may be negatively charged groups, for instance, sulfate groups, neutral groups, or positively charged groups, for instance, quaternary ammonium groups. In the case where the substituent group is sulfate, it is preferred that the sulfated polysaccharide contains at least one sulfate group per saccharide (glucose) unit.

[0012] The present invention provides the use of a composition in the prevention or reduction of the incidence of adhesions that are formed as the result of an inflammatory response, other than post-operative adhesions, the composition comprising an aqueous solution or suspension or gel formulation of the polysaccharide dextrin.

[0013] Dextrin is a useful material for the production of an adhesion-preventing composition because, *inter alia,* it is non-toxic, cheap and has the ability to hold fluid in a body cavity. It is also readily metabolised within the body.

[0014] In the instance of the inflammatory response being as a result of chemical insult by chemotherapy, the composition suitable for the use of the present invention may be applied to the body cavity prior to the administration of the chemotherapeutic agent, alternatively it may be applied at the same time or after administration of the chemotherapeutic agent

[0015] Preferably, the composition is co-administered in the manner as aforedescribed with one or more agent selected from the group consisting of a chemotherapeutic agent, a gene therapy agent, an antibiotic or antiviral agent or any other agent which causes an inflammatory response.

[0016] Reference herein to gene therapy agent is intended to include a viral vector the vector being an adenovirus, a retrovirus, a herpesvirus, a plasmid, a phage, a phagemid or a liposome or any other vehicle into which the gene therapy product has been inserted.

[0017] Preferably, the composition is allowed to remain in the body cavity for a minimum of 2 to 3 days and especially over the period during which the inflammatory response is at a maximum. More preferably, the composition should remain in the body cavity for a period of up to 7 to 8 days.

[0018] The composition is to be applied to the body cavity in a volume large enough to keep the surfaces apart and/or to dilute chemotactic signals/cells involved in an inflammatory response. For the peritoneum, the volume should preferably be in the range 500-2000 ml and, more preferably, about 1000 ml-1500 ml.

[0019] The composition is to be applied to the appropriate body cavity or area in differing concentrations ideally over a concentration range of 2.5-20% and more ideally over a concentration range of 3-5% and most ideally at about 4% by weight, said concentration range is selected for a specified time span, even more ideally the concentration range is selectively altered over a period of time.

[0020] The composition suitable for the use of the present invention should include a concentration of dextrin which is such that the fluid largely holds in place over the period it resides in the cavity. Where a composition includes 4% by weight of dextrin then a suitable dwell period for one infusion might be of the order of 2 to 3 days. A high concentration is liable to cause ingress of fluid. A second infusion at day 3 may extend the total dwell period from 6 to 7 days.

[0021] Alternatively, a composition having a dextrin concentration of from 12 to 15% by weight may be used in a smaller volume (perhaps about 750 ml) and will be subject to ingress of fluid. However a single infusion might be sufficient for the full 6 to 7 day period.

[0022] It will be appreciated that the concentration of the composition the timing of administration and the dwell time are variable and may be selected according to a user's requirements. For example if a chemotherapeutic agent were to be administered over a period of several weeks then the composition of the present invention may be given for the same or extended duration of the therapy and at least until the inflammatory response had abated/ceased. The variations of a dosing regimen are not intended to limit the scope of the application.

[0023] Comparing dextrin with dextran, the latter has relatively poor biocompatibility. It is subject to immunological hypersensitivity due to its concentration in lymph nodes and its lack of metabolisability. At best, a dextran solution or suspension will act not so much to separate surfaces and therefore prevent adhesions but simply as a lubricant. Dextrin advantageously serves as an osmotic agent, which can maintain the volume of a solution in the peritoneal cavity. The continued presence of the dextrin solution within the cavity serves to separate tissues which otherwise may adhere to each other in addition to dilution of the inflammatory response.

[0024] The composition may include any one or more of the following: a suitable lubricant such as a phosphospholipid; a calcium binding agent such as EDTA or sodium citrate; a hyaluronate; a prostacyclin or an analogue thereof; a glycosaminoglycan; an antibiotic agent or a material/agent which is associated with preventing an infection or build up of bacteria or foreign bodies or the like.

[0025] The composition may also include a fibrinolytic agent or an analogue thereof, an anti-inflammatory agent or an analogue thereof, dextrin sulphate and/or methylene blue.

Brief Description of the Drawings

[0026] The invention will now be described by way of example only with reference to the following Figures and Tables wherein:

Table 1 shows adhesion scores in adriamycin treatment groups receiving differing concentrations of icodextrin compared to controls; and

Table 2 shows the number (%) at each score in adriamycin treatment groups receiving differing concentrations of icodextrin compared to controls.

Table 3 shows overall adhesion scores in the treatment group receiving continuous 0.77 U/ml bleomycin in the presence of Ringer's lactated solution (RLS) by pump.

Table 4 shows overall adhesion scores in the treatment group receiving continuous 0.77 U/ml bleomycin in the presence of 4% icodextrin by pump.

Table 5 shows overall adhesion scores in the treatment group receiving 0.77 U/animal bleomycin as a single bolus in 15ml Ringer's lactated solution (RLS)

Table 6 shows overall adhesion scores in the treatment group receiving 0.77 U/animal bleomycin as a single bolus in 15ml 4% icodextrin.

Table 7 shows overall adhesion scores in the treatment group receiving 0.077 U/animal bleomycin as a single bolus in 15ml Ringer's lactated solution (RLS).

Table 8 shows overall adhesion scores in the treatment group receiving 0.077 U/animal bleomycin as a single bolus in 15ml 4% icodextrin.

Figure 1 represents a bar chart of number of animals with specific adhesion scores in adriamycin treatment groups receiving differing concentrations of icodextrin compared to controls;

Figure 2 represents a bar chart of the overall adhesion scores per animal in the six different treatment protocol groups receiving bleomycin.

Figure 3 represents a bar chart of the adhesion score of each animal in each of the six different treatment protocol groups receiving bleomycin.

Detailed Description of the Embodiments of the Invention

[0027] We have conducted experiments to evaluate the effect of administration three concentrations (4%, 15% or 20%) of icodextrin in comparison with a control group receiving phosphate buffered saline (PBS) on the formation of adhesions in response to i.p. adriamycin administration in rats. In addition, we provide data on the effect of adhesion formation in rats as a result of administration of bleomycin in conjunction with Ringer's lactated solution (RLS) or 4% icodextrin, either by dosing continuously by pump or as a single bolus dose.

PROTOCOL

[0028] Animals: . Female Sprague Dawley rats, 175 to 200 grams, were purchased from and quarantined in the USC Vivaria for at least 2 days prior to use. The animals were housed on a 12:12 light:dark cycle with food and water available ad libitum. Thirty animals were used for the adriamycin experiments and forty for the bleomycin experiments.
[0029] Materials: The 4% [wt/vol], 15% or 20% icodextrin were supplied by ML Laboratories PLC. The sutures used to close the muscle and skin were 4-0 Ethilon (Ethicon, Somerville, NJ). The sutures to secure the tubing and pump were 5-0 Ethilon. Alzet miniosmotic pumps (10 µl/hour, 2 ml, Model 2M1) were purchased from Alza Corporation (San Francisco, CA). Polyethylene tubing was purchased from Clay Adams (VWR, Irvine CA).
[0030] Surgical Procedure: Animals were anesthetized with a mixture of 85 mg/kg ketamine hydrochloride and 5 mg/kg Rompum intramuscularly. Following preparation for sterile surgery, a small incision was made at the midline. In animals in which a pump was placed, a polyethylene catheter (Clay Adams polyethylene tubing PE-60 ID 0.76 mm (0.030") OD 1.22 mm (0.048")) was introduced into the peritoneal cavity and sutured to the sidewall with 5-0 Ethilon. The pump was filled with 23.2 µg/ml Adriamycin (10 µl/hour over in life phase) or with 0.77 U/ml bleomycin (0.0077 U/hour) and placed in the subcutaneous space. The catheter was then attached to the pump and the midline muscle incision was closed around the catheter. Prior to closure of the last stitch, a 21-gauge catheter was introduced into the peritoneal cavity and a purse string suture was placed through the muscle around the catheter. In the adriamycin

experiments, 20 ml of solution (4%, 15% or 20% icodextrin or PBS) were administered. In the bleomycin experiments 15 ml of RLS or 4% icodextrin were administered to the treatment groups as stated below. Subsequently, the skin incision was then closed with 4-0 Ethilon sutures.

Group	Bleomycin conc.	Mode of Administration	Co-administered compound
1	0.77 U/ml	Pump	RLS
2	0.77 U/ml	Pump	Icodextrin
3	0.77 U/ml	Fluid (bolus)	RLS
4	0.77 U/ml	Fluid (bolus)	Icodextrin
5	0.077 U/ml	Fluid (bolus)	RLS
6	0.077 U/ml	Fluid (bolus)	Icodextrin

[0031] Seven days after the initiation of adriamycin treatment and nine days after bleomycin treatment, the rats were euthanized by CO_2 and the extent of adhesion formation was evaluated. Adhesions were expected in the areas around the catheter, between the catheter and intestines or liver and between the lobes of the liver. The overall score was based upon the extent of adhesion formation and the number of sites involved in adhesion formation. This was a qualitative assessment based upon the appearance of the abdomen. The scoring system used to report adhesions in these studies is as follows:

0 No adhesions found in the peritoneal cavity
0.5+ Only a few, very filmy adhesions between the sidewall and catheter. Essentially no or very little fibrin-like substance covering the catheter
1.0+ Adhesions present between the sidewall and catheter with mild bowel or liver adhesions (to itself not catheter). Mild fibrin-like covering around catheter.
1.5+ Adhesions involving the liver and/or bowel and catheter. The covering on the catheter is more extensive than 1.0+.
2.0+ Adhesions as with 1.5+ with increase fibrin covering on the catheter and increased density of liver and/or bowel adhesions to catheter.
2.5+ Adhesions as described in 2.0+ but are more dense.
3.0+ More sites are involved in adhesions than in animals scored with 2.5+
4.0+ Sites (catheter to sidewall, liver, bowel and organs to themselves) as in 3.0+, but more than one site involves dense, nondissectable adhesions.

[0032] The animals were evaluated by two independent, blinded observers. If there was a disagreement as to the score, the higher one was given. Overall adhesion scores were given that took into account all of the adhesion and fibrosis scores listed above.

STATISTICAL METHODS

[0033] Non-parametric statistics were used to analyse the adriamycin data as there were 10 rats per treatment group and results were ordinal data from a scoring system.

[0034] The overall treatment effect was tested using the Kruskal-Wallis test. Further investigations in the presence of a treatment effect were to investigate each icodextrin concentration compared to the control group, using the Wilcoxon rank sum statistic.

Adriamycin Results

[0035] Ten animals pre treatment group were studied. In the control group and the 4% icodextrin group all animals were assessed for adhesion formation. In the 15% icodextrin group 1 rat was not assessed. Five (50%) of the rats in the 20% icodextrin group were euthanized early due to abdominal bulging and were not scored. The number of animals (%) at each score is presented in Table 2.

[0036] There was an overall treatment effect($p<0.001$), using the Kruskal-Wallis test. Using the Wilcoxon rank sum statistic differences between each icodextrin group and the control group were investigated. There were significant differences between the 4% icodextrin group ($p<0.01$), the 15% icodextrin group ($p<0.01$), 20% icodextrin group ($p<0.05$) and the control group. Adhesion scores were lower in all the icodextrin groups than in the control groups

(Figure 1). All adhesion scores in the icodextrin groups were 1.5 or less (Table 1).

[0037] From our studies we have shown that all three icodextrin groups had significantly lower adhesion scores than the crystalloid solution and that administration of icodextrin at the end of the procedure reduced the formation of adhesions formed as a result of chemotherapy. The efficacy of the reduction of adhesion formation increased as the percentage of icodextrin was increased. However in the group of animals that received 20% icodextrin, half of the animals were euthanized early due to abdominal bulging and were not scored.

Bleomycin Results

[0038] Continuous administration of bleomycin resulted in substantial adhesions in the presence of Ringer's lactated solution (RLS), Table 3 Group 1, Rank 7.8±0.9. In the presence of icodextrin, this was significantly reduced (Table 4, Rank 3.2±1.0, p = 0.02). Administration of bleomycin in a single bolus resulted in less fibrosis (Table 5, Rank 8.0±0.0 and Table 7, Rank 6.5±1.4). However, at the higher concentration of bleomycin, administration of the chemotherapeutic in the presence of icodextrin significantly reduced adhesion formation (Table 6, Rank 3.0±0.0, p = 0.004 and Table 8, Rank 4.5±0.0, p = 0.18). The p values given are for comparison of the ranks of the most comparable RLS and icodextrin-treated groups using the Wilcoxon signed rank test. The results are tabulated below:

Bleomycin Conc	Dose Regimen	Rank Score RLS	Rank Score 4% icodextrin	P value
0.77 U/ml	pump	7.8 ±.0.9	3.2 ± 1.0	P=0.02
0.77 U/ml	bolus	8.0 ± 0.9	3.0 ± 0.0	P = 0.004
0.077 U/ml	bolus	6.5 ±1.4	4.5 ± 0.0	P= 0.18

[0039] In summary, the adhesiogenic effect of a high dose of bleomycin (0.77 U/ml) administered either continuously by pump in either RLS or 4% icodextrin (Groups 1 and 2) or as a single bolus dose (Groups 3 and 4) were compared. In addition a comparison between high dose (Groups 3 and 4) and a ten fold lower dose of bleomycin (0.077 U/ml; Groups 5 and 6) as a single bolus doses were compared. Our results have shown that 4% icodextrin is significantly more effective than RLS at preventing adhesion formations as a result of dosing with 0.77 U/ml bleomycin, irrespective of the dosing regimen being continous or by a single bolus. No differences between 4% icodextrin and RLS was observed at the lower dose of bleomycin (0.077 U/ml) as virtually no adhesions were formed by this concentration of bleomycin.

[0040] The disclosed dextrin composition is therefore useful as preventing adhesion that occur as a result of chemotherapeutic injury and inflammatory responses.

Table 1.

Adhesion Scores in Rats Receiving 20 ml Phoshate Buffered Saline Solution (PBS) or icodextrin			
PBS	**4% icodextrin**	**15% icodextrin**	**20% icodextrin**
1	0.5	0	0
1.5	0.5	0	0
1.5	0.5	0.5	0.5
2	1	0.5	0.5
2	1	1	1.5
2	1	1	
2.5	1.5	1.5	
2.5	1.5	1.5	
3	1.5	1.5	
4	1.5		

Table 2:

Number (%) at each score				
Score	Control	4% icodextrin	15% icodextrin	20% icodextrin
0	0	0	2 (22%)	2 (40%)
0.5	0	3 (30%)	2 (22%)	2 (40%)
1	1 (10%)	3 (30%)	2 (22%)	0
1.5	2 (20%)	4 (40%)	3 (33%)	1 (20%)
2	3 (30%)	0	0	0
2.5	2 (20%)	0	0	0
3	1 (10%)	0	0	0
4	1 (10%)	0	0	0

Table 3:

Group 1: Bleomycin 0.77 U/ml in RLS with pump									
Catheter	Liver	Sidewall	Bowel	Liver -Catheter	Bowel-Catheter	Capsulation	Omentum	Horn-Catheter	Score
3	1	-	-	-	-	2	-	2	2
3	-	-	1	-	-	2	-	3	3
2	-	-	-	-	1	1	-	2	2.0
2	2	-	-	-	3	-	-	-	25
3	2	-	-	-	-	2	-	2	25

Table 4

: Group 2: Bleomycin 0.77 U/ml in 4% icodextrin with pump									
Catheter	Liver	Sidewall	Bowel	Liver-Catheter	Bowel-Catheter	Capsulation	Omentum	Horn-Catheter	Score
2	-	-	-	-	-	-	-	-	0.5
-	-	-	-	-	-	-	-	-	0
3	-	-	-	-	-	-	2	1	2.0
2	-	-	-	-	-	-	-	-	1
1	-	-	-	-	-	1	1**	-	1

Table 5:

Group 3: Bleomycin 0.77 U/rat in RLS 15 ml IP								
Catheter	Liver	Sidewall	Bowel	Liver-Catheter	Bowel-Catheter	Capsulation	Omentum	Horn-Catheter	Score
-	1*	1	-	-	-	-	-	-	0.5
-	1*	-	1	-	-	-	1**	-	0.5
-	1*	-	-	-	-	-	-	-	0.5
-	1*	-	-	-	-	-	1**	-	0.5
-	1*	-	-	-	-	-	1**	-	0.5

Table 6:

Group 4: Bleomycin 0.77 U/rat m 4% icodextrin 15 ml IP								
Catheter	Liver	Sidewall	Bowel	Liver-Catheter	Bowel-Catheter	Capsulation	Omentum	Horn-Catheter	Score
-	-	-	1**	-	-	-	-	-	0
-	-	-	1**	-	-	-	-	-	0
-	-	-	-	-	-	-	-	-	0
-	1*	-	-	-	-	-	-	-	0
-	-	-	1(SI+)**	-	-	-	-	-	0
+SI refers to the involvement of the small intestine.									

Table 7:

Group 5 Bleomycin 0.077 U/rat in RLS 15 ml IP								
Catheter	Liver	Sidewall	Bowel	Liver-Catheter	Bowel-Catheter	Capsulation	Omentum	Horn-Catheter	Score
-	-	-	-	-	-	-	1**	-	0
-	-	-	-	-	-	-	-	-	0
-	-	-	1**	-	-	-	1**	-	0
-	-	-	1	-	-	-	-	-	0.5
-	-	-	1	-	-	-	-	-	0.5

Table 8:

Group 6: Bleomycin 0.077 U/rat in 4% icodextrin 15 ml IP								
Catheter	Liver	Sidewall	Bowel	Liver-Catheter	Bowel-Catheter	Capsulation	Omentum	Horn-Catheter	Score
-	1	-	-	-	-	-	-	-	0
-	-	-	-	-	-	-	-	-	0
-	-	-	-	-	-	-	-	-	0
-	-	-	-	-	-	-	-	-	0
-	-	-	-	-	-	-	-	-	0

* refers to **fibrosis** not adhesion
** refers to **inflammation** not adhesion

Claims

1. The use of a composition comprising an aqueous formulation of dextrin for the manufacture of a medicament for the treatment of adhesions that are formed as a result of an inflammatory response to an agent selected from a chemotherapeutic or gene therapy agent or antibiotic or antiviral agent or an agent which causes an inflammatory response..

2. Use according to claim 1 wherein the aqueous formulation is a solution.

3. Use according to either preceding claim wherein the percentage of α-1,6 linkages in dextrin is less than 10%.

4. Use according to Claim 3 wherein the percentage of α-1,6 linkages in dextrin is less than 5%.

5. Use according to any preceding claim wherein the number average molecular weight (Mn) of dextrin is in the range 1,000 to 30,000.

6. Use according to Claim 5 wherein the Mn of dextrin is in the range 3,000 to 8,000.

7. Use according to any preceding claim wherein the weight average molecular weight (Mw) of dextrin is in the range 3,000 to 50,000.

8. Use according to Claim 7 wherein the Mw of dextrin is from 5,000 to 50,000.

9. Use according to any preceding claim wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12.

10. Use according to any of Claims 1-8 wherein the dextrin contains more than 50% of polymers with a degree of polymerisation (DP) greater than 12.

11. Use according to any preceding claim wherein the dextrin is unsubstituted dextrin.

12. Use according to any of Claims 1-10 wherein the dextrin is substituted by one or more different groups selected from the group consisting of negatively charged groups, sulfate groups, neutral groups, positively charged groups and quaternary ammonium groups.

13. Use according to Claim 12 wherein the dextrin is sulfated dextrin containing at least one sulfate group per saccharide (glucose) unit.

14. Use according to any preceding claim in which the dextrin is present in the composition in an amount of from 2.5-18 % by weight.

15. Use according to Claim 14 in which the dextrin is present in the composition in an amount of from 3-5 % by weight.

16. Use according to either of Claims 14 or 15 in which the dextrin is present in the composition in an amount of about 4 % by weight.

17. Use according to any preceding claim wherein the composition further includes a calcium binding agent.

18. Use according to Claim 17 wherein the calcium binding agent is either EDTA or sodium citrate.

19. Use according to any preceding claim wherein the composition further includes a suitable lubricant.

20. Use according to Claim 19 wherein the lubricant is a phospholipid.

21. Use according to any preceding claim wherein the composition further includes a hyaluronate.

22. Use according to any preceding claim wherein the composition further includes a compound selected from one or more of the following compounds, glycosaminoglycan, an antibiotic agent, prostacyclin or an analogue thereof, a

fibrinolytic agent or an analogue thereof, an anti-inflammatory agent or an analogue thereof, dextnn sulphate, vehicle and/or methylene blue.

23. Use according to any preceding claim wherein the medicament is for a treatment wherein the dextrin is administered before said agent.

24. Use according to any of claims 1 to 22 wherein the medicament is for a treatment wherein the dextrin is administered with said agent.

25. Use according to any of claims 1 to 22 wherein the medicament is for a treatment wherein the dextrin is administered after said agent.

26. Use according to any preceding claim wherein the medicament is for administration into a body cavity.

Patentansprüche

1. Verwendung einer Zusammensetzung, die eine wässrige Dextrin-Zubereitung umfasst, zur Herstellung eines Medikaments zur Behandlung von Adhäsionen, die als Folge einer Entzündungsreaktion auf ein Agens gebildet werden, das ausgewählt ist aus einem Chemotherapeutikum oder Gentherapie-Mittel oder antibiotischen oder antiviralen Agens oder einem Agens, das eine Entzündungsreaktion verursacht.

2. Verwendung gemäß Anspruch 1, worin die wässrige Zubereitung eine Lösung ist.

3. Verwendung gemäß einem der beiden vorangehenden Ansprüche, worin der Prozentsatz von α-1,6-Bindungen im Dextrin weniger als 10 % beträgt.

4. Verwendung gemäß Anspruch 3, worin der Prozentsatz von α-1,6-Bindungen im Dextrin weniger als 5 % beträgt.

5. Verwendung gemäß irgendeinem vorangehenden Anspruch, worin das Molekulargewicht-Zahlenmittel (Mn) von Dextrin im Bereich von 1.000 bis 30.000 liegt.

6. Verwendung gemäß Anspruch 5, worin das Mn von Dextrin im Bereich von 3.000 bis 8.000 liegt.

7. Verwendung gemäß irgendeinem vorangehenden Anspruch, worin die massengemittelte Molekülmasse (Mw) von Dextrin im Bereich von 3.000 bis 50.000 liegt.

8. Verwendung gemäß Anspruch 7, worin die Mw von Dextrin von 5.000 bis 50.000 ist.

9. Verwendung gemäß irgendeinem vorangehenden Anspruch, worin das Dextrin mehr als 15 % Polymere mit einem Polymerisationsgrad (DP) größer als 12 enthält.

10. Verwendung gemäß irgendeinem der Ansprüche 1 - 8, worin das Dextrin mehr als 50 % Polymere mit einem Polymerisationsgrad (DP) größer als 12 enthält.

11. Verwendung gemäß irgendeinem vorangehenden Anspruch, worin das Dextrin unsubstituiertes Dextrin ist.

12. Verwendung gemäß irgendeinem der Ansprüche 1 - 10, worin das Dextrin substituiert ist durch eine oder mehrere verschiedene Gruppen, ausgewählt aus der Gruppe bestehend aus negativ geladenen Gruppen, Sulfatgruppen, neutralen Gruppen, positiv geladenen Gruppen und quartären Ammoniumgruppen.

13. Verwendung gemäß Anspruch 12, worin das Dextrin sulfatiertes Dextrin ist, das mindestens eine Sulfatgruppe pro Saccharid-Einheit (Glucose) enthält -

14. Verwendung gemäß irgendeinem vorangehenden Anspruch, bei welcher das Dextrin in der Zusammensetzung in einer Menge von 2,5 - 18 Gewichts-% vorliegt.

15. Verwendung gemäß Anspruch 14, bei welcher das Dextrin in der Zusammensetzung in einer Menge von 3 - 5

Gewichts-% vorliegt.

16. Verwendung gemäß einem der Ansprüche 14 oder 15, bei welcher das Dextrin in der Zusammensetzung in einer Menge von ungefähr 4 Gewichts-% vorliegt.

17. Verwendung gemäß irgendeinem vorangehenden Anspruch, worin die Zusammensetzung weiterhin einen Calciumbinder einschließt.

18. Verwendung gemäß Anspruch 17, worin der Calciumbinder entweder EDTA oder Natriumcitrat ist.

19. Verwendung gemäß irgendeinem vorangehenden Anspruch, worin die Zusammensetzung weiterhin ein geeignetes Gleitmittel einschließt.

20. Verwendung gemäß Anspruch 19, worin das Gleitmittel ein Phospholipid ist.

21. Verwendung gemäß irgendeinem vorangehenden Anspruch, worin die Zusammensetzung weiterhin ein Hyaluronat einschließt.

22. Verwendung gemäß irgendeinem vorangehenden Anspruch, worin die Zusammensetzung weiterhin eine Verbindung einschließt, die aus einer oder mehreren der folgenden Verbindungen ausgewählt ist, Glycosaminoglycan, einem antibiotischen Agens, Prostacyclin oder einem seiner Analoga, einem fibrinolytischen Agens oder einem seiner Analoga, einem entzündungshemmenden Agens oder einem seiner Analoga, Dextrinsulfat, vehikel und/oder Methylenblau.

23. Verwendung gemäß irgendeinem vorangehenden Anspruch, worin das Medikament einer Behandlung dient, bei der das Dextrin vor diesem Agens verabreicht wird.

24. Verwendung gemäß irgendeinem der Ansprüche 1 bis 22, worin das Medikament einer Behandlung dient, bei der das Dextrin mit diesem Agens verabreicht wird.

25. Verwendung gemäß irgendeinem der Ansprüche 1 bis 22, worin das Medikament einer Behandlung dient, bei der das Dextrin nach diesem Agens verabreicht wird.

26. Verwendung gemäß irgendeinem vorangehenden Anspruch, worin das Medikament zur Verabreichung in eine Körperhöhle dient.

Revendications

1. Utilisation d'une composition comprenant une formulation aqueuse de dextrine pour la fabrication d'un médicament en vue du traitement des adhésions qui sont formées et résultant d'une réponse inflammatoire à un agent choisi parmi un agent de thérapie de gêne ou un agent chémothérapeutique, ou un antibiotique ou un agent antiviral ou un agent qui provoque une réponse inflammatoire.

2. Utilisation selon la revendication 1, **caractérisée en ce que** la formulation aqueuse est une solution.

3. Utilisation selon l'une des revendications précédentes, **caractérisée en ce que** le pourcentage de a-1,6 liaisons dans la dextrine, est inférieure à 10 %.

4. Utilisation selon la revendication 3, **caractérisée en ce que** le pourcentage de a-1,6 liaisons dans la dextrine est inférieure à 5 %.

5. Utilisation selon l'une des revendications précédentes, **caractérisée en ce que** le nombre du poids moléculaire moyen (Mn) de dextrine est dans la gamme de 1000 à 30000.

6. Utilisation selon la revendication 5, **caractérisée en ce que** le Mn de dextrine est dans la gamme de 3000 à 8000.

7. Utilisation selon l'une des revendications précédentes, **caractérisée en ce que** le poids moléculaire moyen en

poids (Mw) de dextrine est dans la gamme de 3000 à 50000.

8. Utilisation selon la revendication 7, **caractérisée en ce que** le Mw de dextrine est entre 5000 et 50000.

9. Utilisation selon l'une des revendications précédentes, **caractérisée en ce que** la dextrine contient plus de 15 % de polymères avec un degré de polymérisation (DP) supérieure à 12.

10. Utilisation selon l'une des revendications 1 à 8, **caractérisée en ce que** la dextrine contient plus de 50 % de polymères avec un degré de polymérisation (DP) supérieure à 12.

11. Utilisation selon l'une des revendications précédentes, **caractérisée en ce que** la dextrine est une dextrine non substituée.

12. Utilisation selon l'une des revendications 1 à 10, **caractérisée en ce que** la dextrine est substituée par un ou plusieurs groupes différents choisis parmi le groupe consistant en des groupes chargés négativement, des groupes sulfates, des groupes neutres, des groupes chargés positivement et des groupes ammonium quaternaires.

13. Utilisation selon la revendication 12, **caractérisée en ce que** la dextrine laisse une dextrine sulfatée contenant au moins un groupe sulfate par unité saccharide (glucose).

14. Utilisation selon l'une des revendications précédentes, **caractérisée en ce que** la dextrine est présente dans la composition en quantité variant de 2,5 à 18 % en poids.

15. Utilisation selon la revendication 14, **caractérisée en ce que** la dextrine est présente dans la composition dans une quantité comprise entre 3 et 5 % en poids.

16. Utilisation selon l'une des revendications 14 ou 15, **caractérisée en ce que** la dextrine est présente dans la composition dans une quantité d'environ 4 % en poids.

17. Utilisation selon l'une des revendications précédentes, **caractérisée en ce que** la composition comprend en outre un agent de liaison calcium.

18. Utilisation selon la revendication 17, **caractérisée en ce que** l'agent de liaison calcium est du EDTA ou du citrate de sodium.

19. Utilisation selon l'une des revendications précédentes, **caractérisée en ce que** la composition comporte en outre un lubrifiant adapté.

20. Utilisation selon la revendication 19, **caractérisée en ce que** le lubrifiant est un phospholipide.

21. Utilisation selon l'une des revendications précédentes, **caractérisée en ce que** la composition comporte en outre un hyaluronate.

22. Utilisation selon l'une des revendications précédentes, **caractérisée en ce que** la composition comporte en outre un composé choisi parmi un ou plusieurs des composés suivants, glycosaminoglycan, un agent antibiotique, prostacycline ou analogue de celui-ci, un agent fibrinolytique ou analogue de celui-ci, un agent anti-inflammatoire ou analogue de celui-ci, sulfate de dextrine, un bleu de méthylène et/ou véhicule.

23. Utilisation selon l'une des revendications précédentes, **caractérisée en ce que** le médicament est pour un traitement dans lequel la dextrine est administrée avant ledit agent

24. Utilisation selon l'une des revendications 1 à 22, **caractérisée en ce que** le médicament est pour un traitement où la dextrine est administrée avec ledit agent

25. Utilisation selon l'une des revendications 1 à 22, **caractérisée en ce que** le médicament est pour un traitement pour lequel la dextrine est administrée après ledit agent

26. Utilisation selon l'une des revendications précédentes, **caractérisée en ce que** le médicament est destiné à l'ad-

ministration dans une cavité du corps.

FIGURE 1

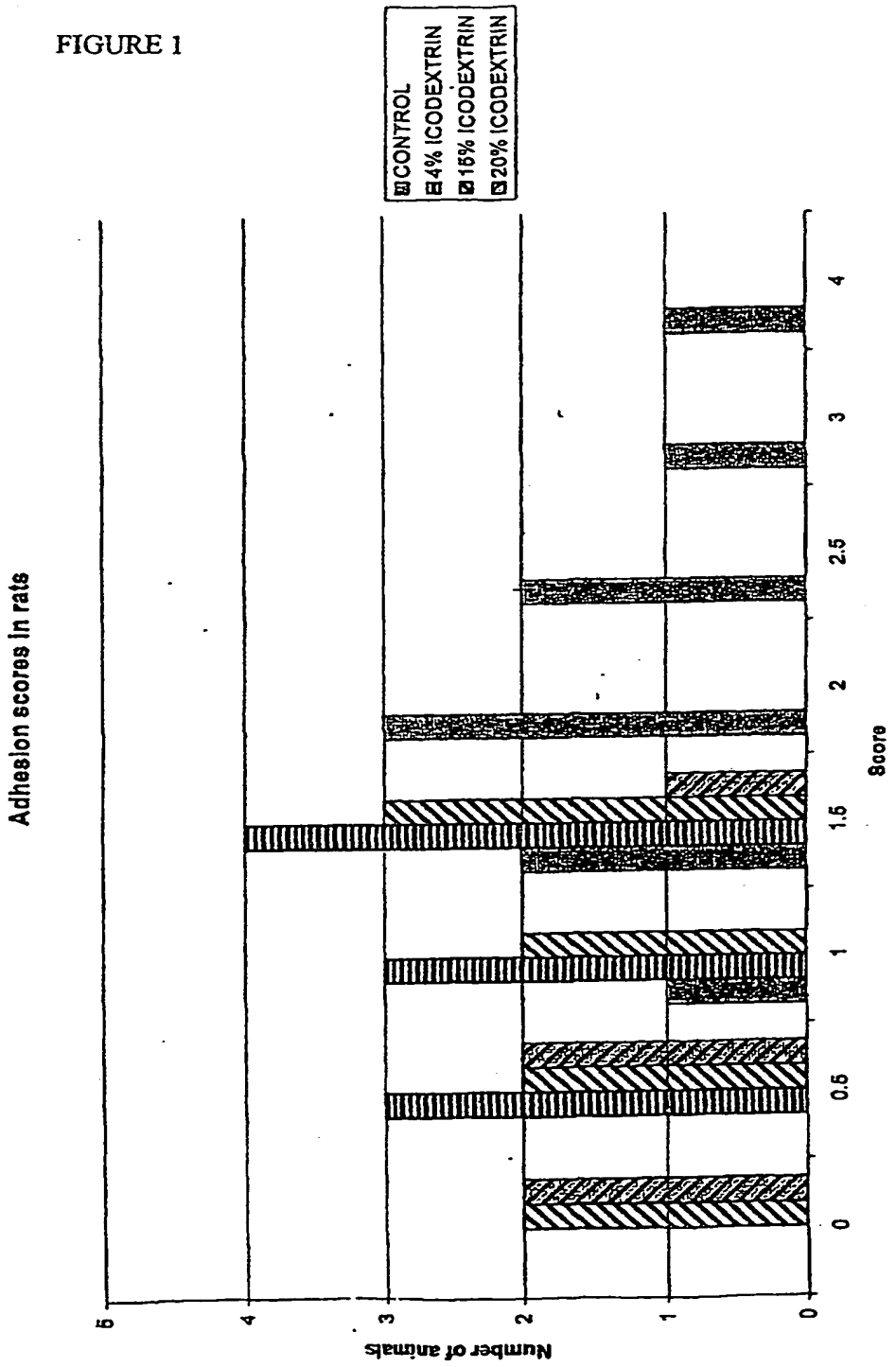

CONTROL
4% ICODEXTRIN
16% ICODEXTRIN
20% ICODEXTRIN
Adhesion scores in rats
Number of animals
Score
0
0.5
1
1.5
2
2.5
3
4
5

FIGURE 2

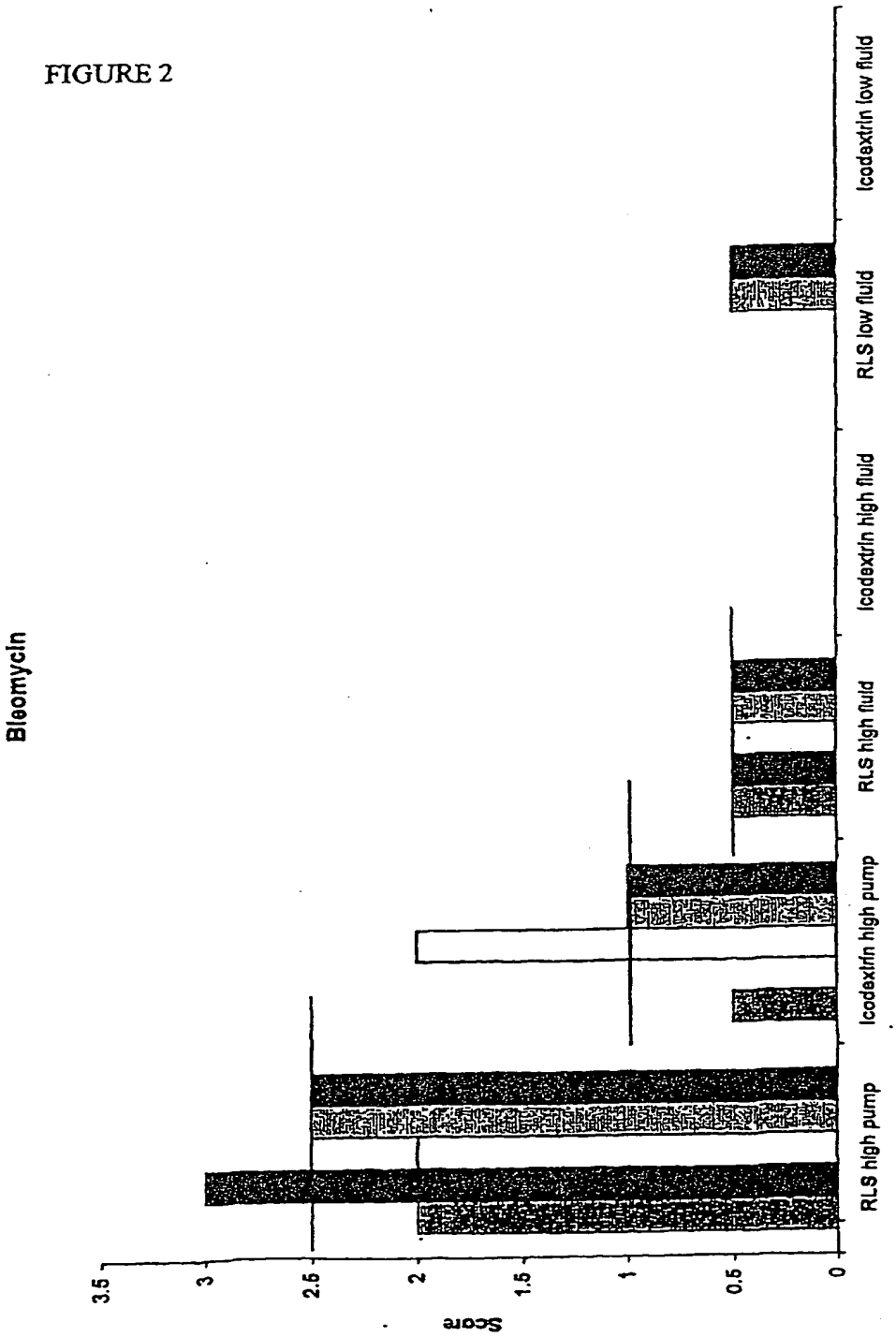
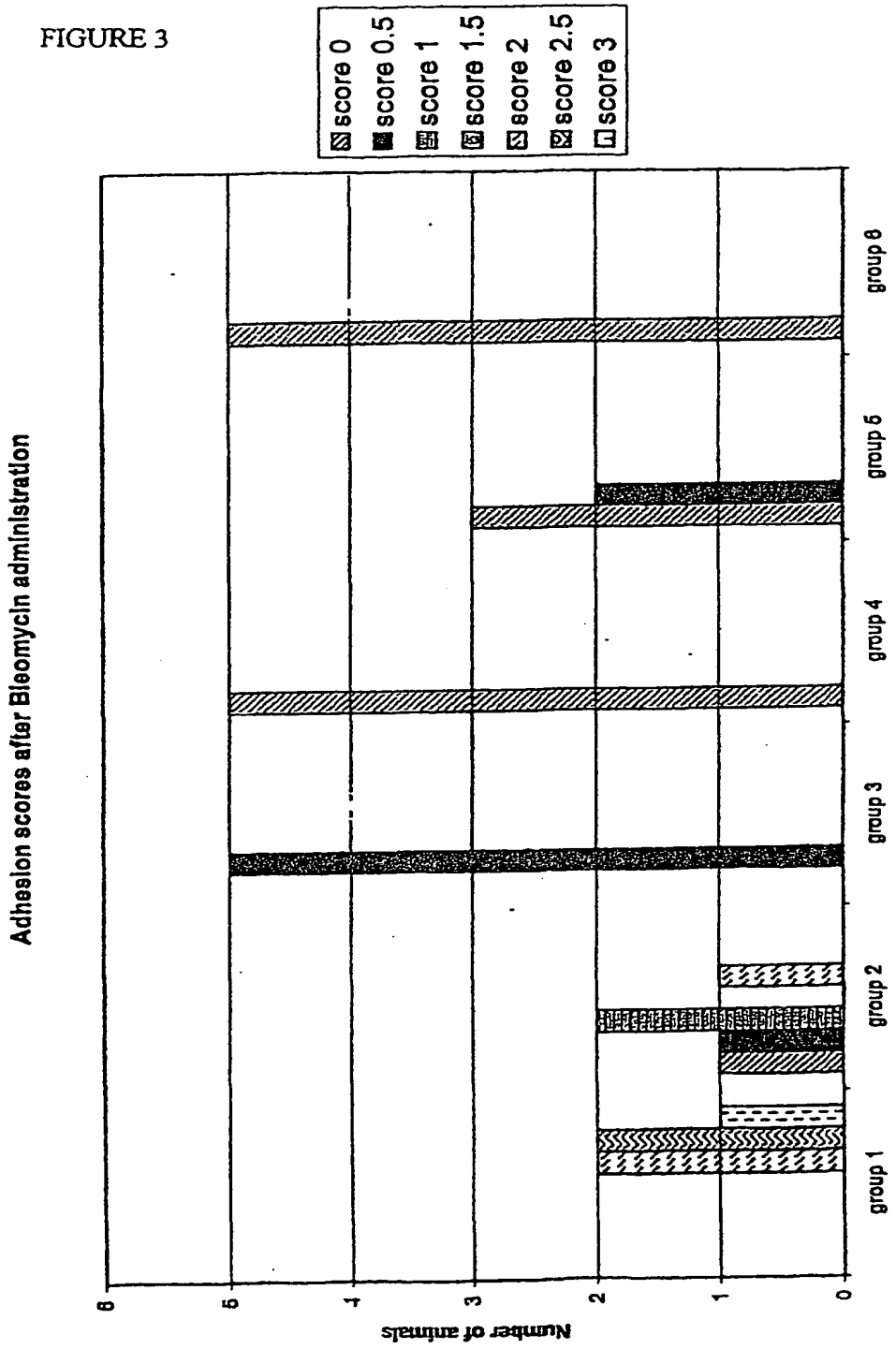

Bleomycin
Score
3.5
3
2.5
2
1.5
1
0.5
0
RLS high pump
Icodextrin high pump
RLS high fluid
Icodextrin high fluid
RLS low fluid
Icodextrin low fluid

FIGURE 3


score 0
score 0.5
score 1
score 1.5
score 2
score 2.5
score 3
Adhesion scores after Bleomycin administration
group 8
group 6
group 4
group 3
group 2
group 1
0
1
2
3
4
5
6
Number of animals

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